C1 Contd

wherein said composition contains from about 0.05% to about 5.0% by weight of said c mpound, in an amount sufficient to enhance oxygen delivery to said tissue.

C2

Claim 35: The method of claim 30, wherein said composition contains from about 0.1% to about 1% by weight of said compound.

Claim 36: The method of claim 30, wherein said composition is a cream, a lotion, a salve, a balm, a roll-on stick, a wash, or a suppository.

Claim 37: The method of claim 30, wherein said composition further comprises butyl benzoate.

REMARKS

Replacement claim 30 is a combination of prior claims 30 & 34. Hence, claim 34 is canceled. Claims 35-37 depended from claim 34, so their dependency requires changing. A showing of changes accompanies this amendment. Claims 30-33 and 35-37 are pending.

The incorporation of claim 34 into claim 30 obviates the anticipation rejection; however, for purposes of good order, applicants are entitled to a decision on their petition.

The examiner rejected claims 30 & 34-37 under 35 USC §103 in view of Huber plus Otsuka. Applicants traverse.

According to the examiner

> "Applicants' rebuttal argument filed August 29, 2002 averring unexpected results have been considered, but are not found persuasive because of reasons discussed above."

The reasons, according to the examiner, are that

> "The data in Table 2 merely demonstrate the duration of octyl ester is longer than that of hexyl ester. This is seen to be an expected effect because the partition coefficient of octyl ester is much higher than that of hexyl ester."

First of all, the examiner has not established that there is a connection between partition coefficients and duration of a pharmaceutical effect.

Further, the following is a direct quote from the primary reference:

> "Of the esters of alcohols having 4-8 carbon atoms, I prefer to use n-hexyl nic tinate."

See column 2, lines 13-15. Huber goes on to state, at lines 15-16

"The hexyl ester is the most effective of the group."

With all due respect to the examiner, the statements made by the inventor must be given deference. If the inventor says C6 is better than C8, applicants rebuttal evidence must be taken as showing that which is unexpected, i.e., that the compound performs for a longer period of time.

Further, the examiner must take all factors into consideration in considering what is claimed. The examiner asserts that , because the C8 compound has a larger coefficient partition, de facto, it must have a more long lasting effect.

Assuming that this unproven statement is true, it ignores other relevant facts. The longer the alkyl ester chain, the larger the partition coefficient. Please see the attached materials. This being the case, it must be noted that compounds where the side chain contains 11 or more carbon atoms do not vasodilate, which is a desired characteristic of the compositions. In other words, duration plus vasodilation are desired. The fact that a compound has a larger partition coefficient does not mean it will vasodilate. This is a fact. Vasodilation is critical to oxygen delivery. The C8-C10 compounds simply work better. Huber expressly dismisses compounds where the alkyl group is larger than 8 carbons (see column 2, lines 11-12), and as has been pointed out, teaches away from C8 because he expressly states C6 is better.

In view of the foregoing, withdrawal of the rejection, and allowance of this application are believed proper and is urged.

Respectfully submitted,

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NIAD 214.1 JEL/NDH (10103730)

VIA FACSIMILE

I hereby certify that this correspondence is being facsimile transmitted to the Commissioner of Patents and Trademarks, Washington, D.C. 20231 on February 20, 2003.

Fulbright & Jaworski L.L.P.

Lauri Oles

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Applicant	:	Elaine L. Jacobson, et al.
Serial No.	:	09/834,228
Filed	:	April 12, 2001
For	:	METHODS AND COMPOSITIONS USEFUL IN ENHANCING OXYGEN DELIVERY TO CELLS
Art Unit	:	1617
Examiner	:	S. Hui

February 20, 2003

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

SHOWING OF CHANGES

Claim 30: (amended) A method for enhancing delivery of oxygen to a tissue, comprising administering to said tissue a nicotinic acid alkyl ester containing composition, wherein the alkyl group of said nicotinic acid alkyl ester consists of from 8 to 10 carbon atoms, wherein said composition contains from about 0.05% to about 5.0% by weight of said compound, in an amount sufficient to enhance oxygen delivery to said tissue.

Claim 35: (amended) The method of claim 30 [34], wherein said composition contains from about 0.1% to about 1% by weight of said compound.

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Claim 36: (amended) The method of claim 30 [34], wherein said composition is a cream, a lotion, a salve, a balm, a roll-on stick, a wash, or a suppository.

Claim 37: (amended) The method of claim 30 [34], wherein said composition further comprises butyl benzoate.

Respectfully submitted,

FULBRIGHT & JAWORSKI, L.L.P.

Norman D. Hanson, Esq.
Registration No. 30,946

KowWin (LogKow) Log P Calculation:

SMILES : n1cc(C(=O)OCCCCCC)ccc1
CHEM : 3-Pyridinecarboxylic acid, hexyl ster
MOL FOR: C12 H17 N1 O2
MOL WT : 207.27

TYPE	NUM	LOGKOW v1.66 FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	1	-CH3 [aliphatic carbon]	0.5473	0.5473
Frag	5	-CH2- [aliphatic carbon]	0.4911	2.4555
Frag	5	Aromatic Carbon	0.2940	1.4700
Frag	1	Aromatic Nitrogen	-0.7324	-0.7324
Frag	1	-C(=O)O [ester, aromatic attach]	-0.7121	-0.7121
Factor	1	Pyridine ring (non-fused) correction	-0.1621	-0.1621
Const		Equation Constant		0.2290
			Log Kow =	3.0952

LogKow Estimated Log P: 3.10

Experimental Database Structure Match:
Name: n-Hexyl nicotinoate
CAS Registry Number : 023597-82-2
Experimental Log Kow: 3.51
Experim. Reference : Houk,J & Guy,RH (1988)

C6

http://esc.syrres.com/interkow/interkow.exe?CAS=23597-82-2&submit=Submit+CAS 08/14/2002

KowWin (LogKow) Log P Calculation:

SMILES : O=C(c1cnccc1)OCCCCCCCCC
CHEM : 3-Pyridinecarboxylic acid, nonyl ester
MOL FOR: C15 H23 N1 O2
MOL WT : 249.36

TYPE	NUM	LOGKOW v1.66 FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	1	-CH3 [aliphatic carbon]	0.5473	0.5473
Frag	8	-CH2- [aliphatic carbon]	0.4911	3.9288
Frag	5	Aromatic Carbon	0.2940	1.4700
Frag	1	Aromatic Nitrogen	-0.7324	-0.7324
Frag	1	-C(=O)O [ester, aromatic attach]	-0.7121	-0.7121
Factor	1	Pyridine ring (non-fused) correction	-0.1621	-0.1621
Const		Equation Constant		0.2290
			Log Kow =	4.5685

LogKow Estimated Log P: 4.57

C9

http://esc.syrres.com/interkow/interkow.exe?CAS=98841-58-8&submit=Submit+CAS 08/14/2002

KowWin (LogKow) Log P Calculati n:

SMILES : O=C(c1cccnc1)OCCCCCCCCCC
CHEM : 3-Pyridinecarboxylic acid, decyl ester
MOL FOR: C16 H25 N1 O2
MOL WT : 263.38

TYPE	NUM	LOGKOW v1.66 FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	1	-CH3 [aliphatic carbon]	0.5473	0.5473
Frag	9	-CH2- [aliphatic carbon]	0.4911	4.4199
Frag	5	Aromatic Carbon	0.2940	1.4700
Frag	1	Aromatic Nitrogen	-0.7324	-0.7324
Frag	1	-C(=O)O [ester, aromatic attach]	-0.7121	-0.7121
Factor	1	Pyridine ring (non-fused) correction	-0.1621	-0.1621
Const		Equation Constant		0.2290
			Log Kow =	5.0596

LogKow Estimated Log P: 5.06

C10

http://esc.syrres.com/interkow/interkow.exe?CAS=5338-17-0&submit=Submit+CAS 08/14/2002

KowWin (LogKow) Log P Calculation:

SMILES : O=C(c1cccnc1)OCCCCCCCCCCCC
CHEM : 3-Pyridinecarboxylic acid, dodecyl ester
MOL FOR: C18 H29 N1 O2
MOL WT : 291.44

TYPE	NUM	LOGKOW v1.66 FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	1	-CH3 [aliphatic carbon]	0.5473	0.5473
Frag	11	-CH2- [aliphatic carbon]	0.4911	5.4021
Frag	5	Aromatic Carbon	0.2940	1.4700
Frag	1	Aromatic Nitrogen	-0.7324	-0.7324
Frag	1	-C(=O)O [ester, aromatic attach]	-0.7121	-0.7121
Factor	1	Pyridine ring (non-fused) correction	-0.1621	-0.1621
Const		Equation Constant		0.2290
			Log Kow =	6.0418

LogKow Estimated Log P: 6.04

C12

http://esc.syrres.com/interkow/interkow.exe?CAS=3612-78-0&submit=Submit+CAS 08/14/2002

KowWin (LogKow) Log P Calculation:

SMILES : O=C(c1cnccc1)OCCCCCCCCCCCCCCCC
CHEM : 3-Pyridinecarboxylic acid, hexadecyl ester
MOL FOR: C22 H37 N1 O2
MOL WT : 347.55

TYPE	NUM	LOGKOW v1.66 FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	1	-CH3 [aliphatic carbon]	0.5473	0.5473
Frag	15	-CH2- [aliphatic carbon]	0.4911	7.3665
Frag	5	Aromatic Carbon	0.2940	1.4700
Frag	1	Aromatic Nitrogen	-0.7324	-0.7324
Frag	1	-C(=O)O [ester, aromatic attach]	-0.7121	-0.7121
Factor	1	Pyridine ring (non-fused) correction	-0.1621	-0.1621
Const		Equation Constant		0.2290
			Log Kow =	8.0062

LogKow Estimated Log P: 8.01

C 16

http://esc.syrres.com/interkow/interkow.exe?CAS=66170-39-6&submit=Submit+CAS 08/14/2002